Comparison of Intravenous and Inhaled Terbutaline in the Treatment of Asthma*

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In a double-blind crossover controlled study, intravenous (IV) or nebulized terbutaline was given to eight patients with moderately severe asthma on two separate days. Four incremental doses of terbutaline were given by each route to establish a maximal effect. Both routes of administration produced significant increases in FEV_1, FVC, PEFR, $MEF_{50\%}$ single-breath TLC, and effective pulmonary blood flow. A decrease in slope of alveolar argon plateau was observed with both routes, but helium responsiveness showed variable changes with no significant or consistent effect seen. There was no significant difference between responses to incremental doses and maximal response apart from pulse rate, which rose during IV treatment. These results showed that the IV route had no advantage in terms of effectiveness or site of action over the inhaled route. Since IV treatment can produce systemic side effects, inhaled bronchodilator therapy should be used as the route of choice.

Bronchodilators have been used to treat asthma for many years, but there is still controversy about the best route of administration and the indications for each route. There are many arguments in favor of inhalation therapy, which delivers the bronchodilator to the target organ, and thus keeps the plasma level to the minimum and reduces the likelihood of systemic side effects. Equal bronchodilatation with fewer side effects from salbutamol has been shown for the inhaled route by Bloomfield et al[1] in severe acute asthma and by Spiro et al[2] in moderately severe asthma.

There are, however, potential disadvantages to the inhaled route, the first being that its effectiveness might suffer with increasing airways obstruction as aerosol penetration and distribution become less efficient. This mechanism was invoked to explain the finding by Williams and Seaton[3] of greater effect with salbutamol using the intravenous (IV) route in patients with severe acute asthma. Another possible objection to the inhaled route is that the aerosol is likely to be deposited preferentially in central and larger airways.[4]

Larsson and Svedmyr[5] have suggested that systemic salbutamol has an effect on small airways as well as on the large airways predominantly involved in the aerosol response. Detroyer et al[6] have further suggested that IV and high-dose aerosol fenoterol have an additional systemic effect of relaxation of retractile elements in the lung parenchyma and alveolar ducts.

This study sets out to examine the effectiveness of a bronchodilator, terbutaline, with respect to its route of administration and site of action both within the airway and, by measurements of gas transport, at the lung periphery. The study compares dose-response relationships between the two routes of administration in patients with moderately severe asthma to assess the effect of clinically important airways obstruction on bronchodilator response.

Patients

Eight patients with bronchial asthma in a stable, moderately severe state were investigated following recovery from a severe attack of asthma. Informed consent was obtained from all patients. All had previously demonstrated at least 20 percent reversibility in their airways obstruction after receiving inhaled bronchodilator. The group consisted of six women and two men. Their mean age was 39 years (range, 19 to 56 years). Seven of the subjects were atopic, as judged by positive skin prick tests to common allergens, and none had chronic bronchitis. In addition to oral and inhaled bronchodilator medication, all were receiving oral corticosteroids, the dose of which was kept constant throughout the study. The mean FEV_1 on entry to the study was 1.36 L (range, 0.48 to 1.75 L) or 48 percent predicted (range, 15 percent to 67 percent predicted).

Methods

Flow volume loops were performed during maximal forced expiration, using a dry wedge spirometer (Floop 1 TM pulmonary function studies system, Oldelft). These were obtained with the subject breathing air and again after quiet breathing of a gas mixture of 80 percent helium and 20 percent oxygen for three minutes. The indices measured on the flow volume loops were forced expired volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEFR), maximal midexpiratory flow rate (MMFR), and maximal expiratory flow at 50 percent of the vital capacity (MEF_{50}). Helium responsiveness was assessed as the percentage increase in MEF_{50} of the helium-oxygen flow volume

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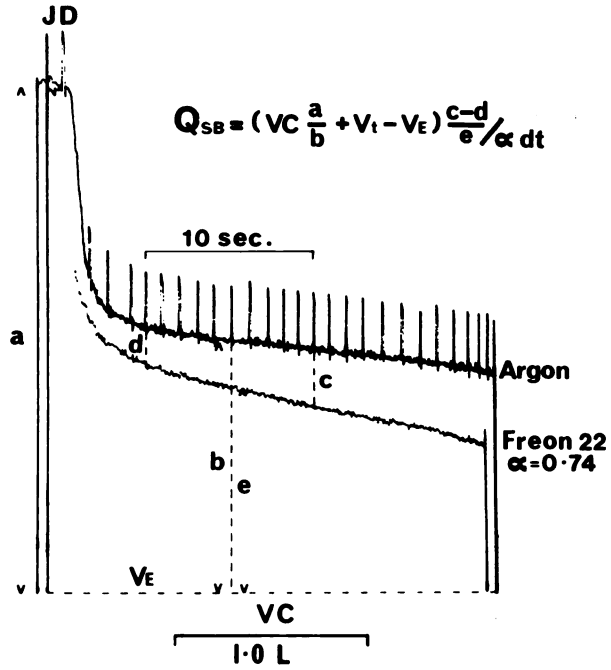

FIGURE 1. Single-breath record obtained from one subject. Gas concentrations recorded against expired volume. 1-sec time signal superimposed as sharp pulsatile deflection on argon trace. Slope of alveolar plateau calculated as percentage change in argon concentration between 750 and 1,250 ml expired. Effective pulmonary blood flow ($\dot{Q}_{sb}$) calculated using equation shown from vital capacity (VC), pulmonary tissue (VT) estimated from data of Sackner et al,[17] volume expired up to point of measurement (VE), gas solubility coefficient (α), and linear measurements (a-e) made on records.

loop compared with that of the corresponding one breathing air.

The effects of terbutaline on pulmonary blood flow were measured by a rebreathing method introduced by Cander and Forster[7] and used more recently by Petrini and Hyde,[8] and also by the single-breath method originated by Krogh and Linhard[9] and further developed by Denison and coworkers.[10,11] One potential advantage of the single-breath method in asthma is that it produces less effect on airway caliber resulting from the maneuver itself than does vigorous rebreathing, which often induces bronchoconstriction.

The single-breath and rebreathing estimates of effective pulmonary blood flow ($\dot{Q}_{sb}$, $\dot{Q}_{rb}$) and measurement of the evenness of ventilation were made using a gas mixture containing low concentrations of the insoluble gas argon (< 5 percent) and the soluble gas difluoromonochloromethane, Freon 22 (< 3 percent). The gas concentrations were monitored at the lips using a mass spectrometer (MGA 007, TC Centronics, Ltd) and permanent records obtained with an XY recorder (Bryans 2600 A3). The slope of the alveolar plateau (phase III), and gas dilution estimates of the accessible gas volume at total lung capacity (VA) were measured from the argon tracings obtained during the single-breath maneuver. In this, gas concentrations were recorded against expired volume measured by a water-filled spirometer (Godart NV), during expiration at a slow constant rate following a vital capacity inspiration of the gas mixture. The slope of the alveolar plateau was measured as the percentage change in argon concentration between 750 ml and 1,250 ml of expired volume. The VA was calculated as the product of the VC and the ratio of the inspired to the mean expired argon concentration (derived by dividing the planimetrically measured area under the argon trace by the VC to give a volume-weighted average of expired concentration).

In the rebreathing procedure, the subject inspired from a bag containing the gas mixture and then rebreathed from the bag at as rapid a rate as his airways obstruction would comfortably permit.

The initial bag volume was chosen using the patient's FEV_1 and FVC so that the subject rebreathed a large proportion of his VC with a 1- to 3-sec cycle. Gas concentrations were measured at the lips and recorded against time. Effective pulmonary blood flow was measured from the divergence of the soluble and insoluble gas concentrations in the time before recirculation occurred. Typical records and the measurements and equations used are shown for the single-breath procedure in Figure 1, and for the rebreathing procedure in Figure 2.

These investigations were performed in the following order: (1) pulse and blood pressure measurement; (2) single-breath argon-Freon 22 procedure, (3) flow volume loops breathing air, (4) flow volume loops after helium-oxygen, and (5) rebreathing argon-Freon 22 procedure.

The rebreathing maneuver was performed last in the series because of the tendency for it to produce changes in the airway caliber. In normal subjects, single-breath and re-

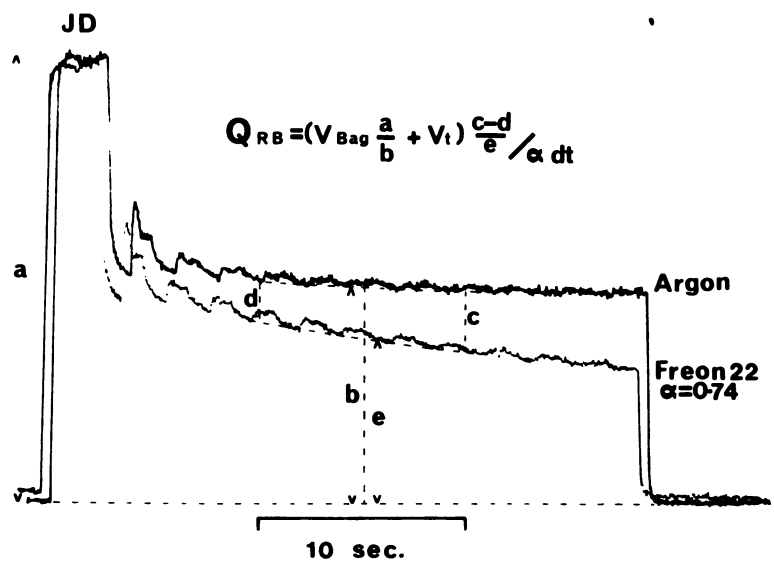

FIGURE 2. Rebreathing record from one subject. Gas concentrations recorded against time. Effective pulmonary blood flow ($\dot{Q}_{rb}$) calculated using equation shown from volume of rebreathing bag (V_{bag}), pulmonary tissue volume (VT), and gas solubility coefficient (α), and the linear measurements (a-e) made in records.

breathing measurements of effective pulmonary blood flow are reproducible within ±5 percent (SD). Normal values for sitting adults are 7 to 8 L/min.[11]

Studies

The study was performed using a double-blind crossover randomized design. Preceding a test day, no bronchodilators were given by the inhaled route for at least six hours, or by the oral or parenteral routes for at least 12 hours. Terbutaline, 2.5 mg/ml, and placebo for inhalation, and terbutaline, 0.125 mg/ml, and placebo for IV injection, were prepared in identical containers and labeled by code number only.

On the first day of the study, a four-stage dose response curve was constructed for either IV or inhaled terbutaline, and on the second day the alternate route was used. On each day, after basal investigations were performed at least twice, 15 minutes apart, to establish a stable baseline, 1 ml of a solution containing either terbutaline, 2.5 mg, or placebo was given via a Bird nebulizer. At the same time, either placebo solution or terbutaline, 0.125 mg, diluted in normal saline solution was infused slowly into an indwelling IV cannula over five minutes. Pulse, blood pressure, and flow volume loops breathing air were recorded immediately after drug administration and at five-minute intervals until a plateau in FEV_1 was obtained. When this occurred, a full set of investigations was performed and the next inhalation procedure and injection given. In this way, four equal increments of the drug were given, accruing to a total dose of 10 mg by inhalation or 0.5 mg IV. The plateau effect after each dose was usually seen after 15 to 20 minutes, the whole study on any day thus being completed in about two hours. The route of administration for the first day was randomly chosen and remained constant throughout that day. The active drug was given by the alternative route on the following day, provided that the baseline FEV_1 was within 10 percent of that on the first day. Responses were analyzed using the Student *t* test for paired values and the Mann-Whitney ranking test.

Results

Basal values for the two days of the study were not significantly different for any of the indices measured. Both IV and inhaled routes of administration of terbutaline produced significant increases in FEV_1, FVC, PEFR, MMFR, and MEF_{50}. Both routes also produced a significant rise in VA and a fall in the slope of the alveolar plateau. These changes are shown graphically in Figures 3 and 4. The effect on the helium responsiveness of the MEF_{50} was variable, and although several patients showed increases, the mean responses of the whole group were not significantly different from the basal values. Both routes of administration also produced significant increases in effective pulmonary blood flow as measured by both single breath and rebreathing techniques.

Using the single-breath method, $\dot{Q}_{eff}$ showed a maximum increase from a basal value of 3.34 ± 1.56 L/min by 1.52 ± 0.88 L/min after inhaled terbutaline and from 3.38 ± 0.74 L/min by 1.54 ± 0.92 L/min after IV terbutaline. The corresponding values for the rebreathing method were 3.26 ± 0.75 L/min increasing by 0.59 ± 0.46 L/min after inhaled terbutaline and 3.51 ± 0.75 L/min increasing

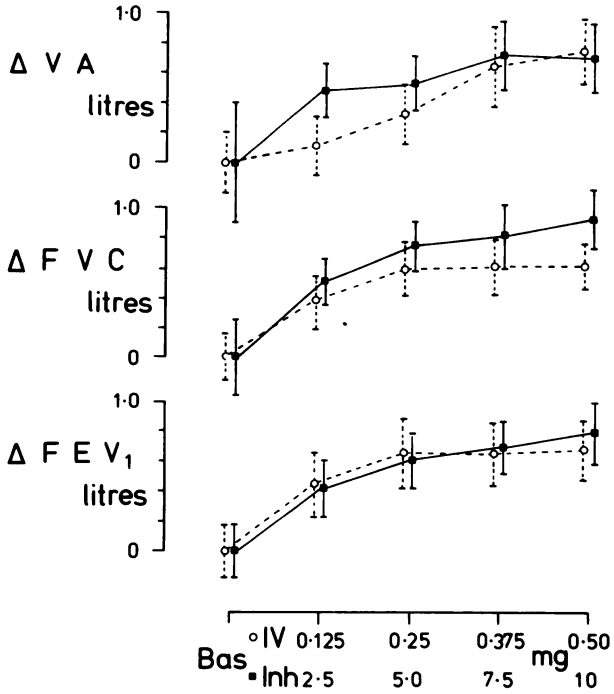

Figure 3. Comparison of increases in FEV_1, FVC, and VA between intravenous and inhaled routes of administration. Mean±SE.

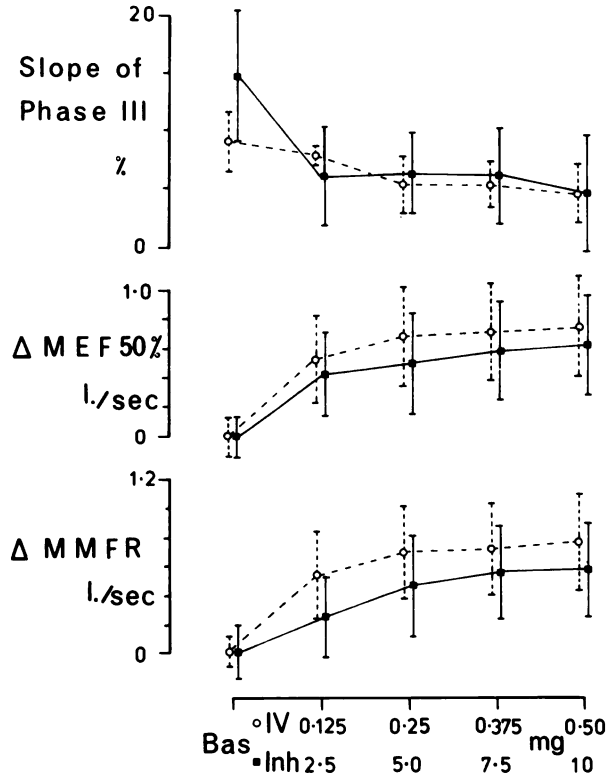

Figure 4. Comparison of the increases in MMFR and MEF_{50} and effect on slope of alveolar plateau of two routes of administration. Mean ± 1 SE.

by 0.71 ± 0.76 L/min after IV terbutaline. Effective blood flow per unit of ventilated lung volume ($\dot{Q}_{eff}$/VA) was derived by dividing individual blood flow values by their corresponding estimate of VA. This index increased significantly after terbutaline by both routes of administration for the single-breath studies, but did not change significantly for the rebreathing estimates. Pulse rate increased significantly after IV terbutaline, but fell slightly when the drug was given by inhalation. Only very small changes in blood pressure were observed and were not significantly different from basal values. The changes in effective pulmonary blood flow, pulse, and blood pressure are shown in Figure 5.

There were no significant differences between the effects of terbutaline by the IV and inhaled routes when comparisons were made at each of the four dosage intervals for any of the indices measured except pulse rate. The pulse rate was significantly higher after the IV route at every dose interval than for the inhaled route, when it actually fell slightly. Comparison of the maximal effects of the drug at any dose level between the two routes of administration again showed no significant difference for any of the variables measured except for pulse rate. Analysis of the results of individual patients failed to show any tendency for those with more severe airways obstruction within the group to show a greater effect produced by either route of administration.

The dose response relationship for each route of administration was analyzed by comparing the cumulative effects at each dose interval within that route. For the IV route most of the indices assessed were close to their maximal effect by the second dose, the further increments producing only small extra improvements that were usually not significant. An accumulated dose of 0.25 mg IV thus produced most of the effects obtainable by this route. For the inhaled route most indices showed continuing improvement right up to the last increment, which represented a total accumulated dose of 10 mg, *ie,* a plateau effect was not observed with this route of administration. Apart from mild tremor experienced by one patient on both days of the study, no other side effects were experienced by the patients.

Discussion

The results do not show any difference between the route of administration in terms of the ventilatory response produced by terbutaline. In other words, bronchodilator activity appeared independent of route of administration, in this group of patients with moderately severe airways obstruction. No difference could be seen in site of activity of the bronchodilator, with an equivalent response being seen for tests of large and small airways. These results suggest that a bronchodilator, whether delivered parenterally or by aerosol, can affect all parts of the tracheobronchial tree to produce equivalent bronchodilation, even in the presence of moderately severe airways obstruction.

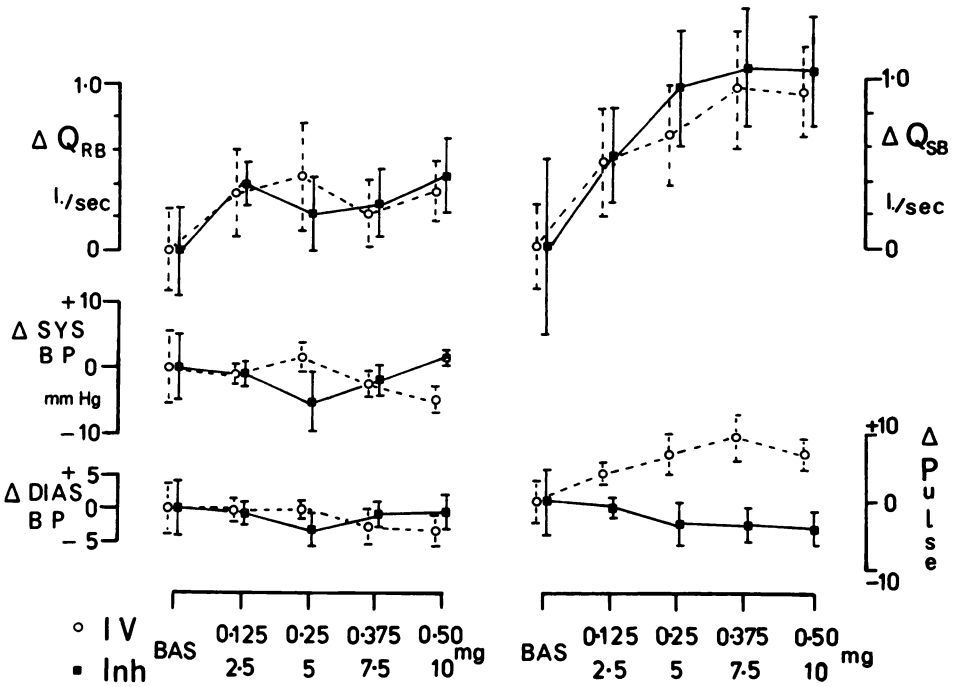

Figure 5. Comparison of effects on effective pulmonary blood flow, pulse and blood pressure between two routes of administration. Mean±1 SE.

The distinction between large and small airways obstruction and the realization that asthma may preferentially affect different airways during the natural history of the disease have led to doubts that bronchodilators by inhalation can have as complete and comprehensive an effect as those delivered by mouth or parenterally.[4,5] A number of studies argue that view, including the observations by Hensley et al,[12] which showed isoprenaline by aerosol affecting small airways as opposed to a more central action of aerosol atropine. Studies of exercise-induced asthma have also shown that changes in residual volume that follow exercise can rapidly be reversed by inhaled bronchodilators,[13] and this also suggests a peripheral action of the inhaled salbutamol used in that study. Further work by Wagner et al[14] has shown that inhaled bronchodilators can rapidly affect ventilation–perfusion ratios and arterial blood gases, indicating a distal site of action. Studies carried out in Montreal by Antic and Macklem[15] have shown that inhaled salbutamol can reverse the expiratory flow limitation, which appears to arise in small airways as judged by helium and air flow volume curves. All of these studies, therefore, have indicated that the inhaled route can effectively achieve peripheral as well as central bronchodilatation, and our results, which were designed specifically to examine this matter, support these conclusions. The study by Tashkin et al[4] is difficult to interpret, since only single doses were used, and the nebulized dose was only 0.5 mg, which is very submaximal and not comparable with the subcutaneous dose of 0.5 mg, which is about maximal.

Effective pulmonary blood flow as measured by both single-breath and rebreathing methods increased significantly after both routes of administration. These increases in $\dot{Q}_{eff}$ were greater with the single-breath method. To a large extent, this was due to the increase in ventilated volume (VA), but the index $\dot{Q}_{eff}$/VA or effective blood flow per unit of ventilated volume still showed a significant increase for the single-breath method. The rebreathing method did not show this effect, a difference perhaps related to its own effects on bronchial muscle tone. Although Gayrard et al[16] have demonstrated a bronchoconstrictor effect from even a single deep inspiration, our patients were noticeably more wheezy after performing the rebreathing maneuver, but not after the single-breath test. The increase in blood flow per unit of ventilated lung volume seen by the single-breath method may be due to a small but real increase in cardiac output or to a fall in the mean $\dot{V}/\dot{Q}$ ratio of the accessible lung units, perhaps owing to recruitment of peripheral units with lower $\dot{V}/\dot{Q}$ ratios into the volume accessible in a single inspiration. Wagner et al[14] have demonstrated a similar shift in the distribution of $\dot{V}/\dot{Q}$ ratios in asymptomatic asthmatic subjects after isoprenaline.

The dose response relationships were established to determine the maximal effect by each route of administration and were similar for both routes, although a plateau effect was not achieved by the inhaled route. This was found in an earlier study of both oral and inhaled salbutamol.[5] The similarity of the dose response curve over the doses used shows that the inhaled route can provide effective bronchodilation in the presence of severe airways obstruction, especially when taking into account the fact that only about 20 percent of the dose delivered by nebulizer reaches the lungs.

The other benefit of the inhaled route was clearly shown by the only difference observed between the two routes of administration, *viz*, pulse rate. Although the cardiac output response was the same for both routes, pulse rate increased following IV terbutaline and fell after the delivery of inhaled terbutaline.

Our study, therefore, has shown that route of administration does not significantly influence the scale and effectiveness of the bronchodilation achieved by terbutaline but does influence the likelihood of systemic side effects, as witnessed by the difference in pulse rate. Inhaled bronchodilators can be fully effective in treating airways obstruction in all parts of the tracheobronchial tree and can do so at a dose delivered to the airway that minimizes systemic side effects. This activity can be achieved in patients with moderately severe asthma as well as those with mild to moderate asthma who also respond well to aerosol bronchodilation. Patients with severe acute asthma or status asthmaticus were not included in this study because of the difficulty in performing detailed tests under these circumstances. There was no tendency, however, for those with the most severe airways obstruction to show a greater response to the parenteral route. The findings of Bloomfield et al[1] in severe acute asthma also suggest that our conclusions apply to patients with severe acute asthma as well. Our results therefore give further support to the use of inhaled bronchodilators in the management of asthma and suggest that we should now reexamine the need for giving bronchodilators by any other route.

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